

# Exhibit C

# WHAT'S NEXT FOR MECHANICAL CIRCULATORY SUPPORT AFTER THE IMPRESS SEVERE SHOCK TRIAL?

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**MORTALITY IN PATIENTS** with acute myocardial infarction with cardiogenic shock remains high, despite ongoing advances in treatment.<sup>1-4</sup> While the intra-aortic balloon pump (IABP) has been the most widely short-term mechanical circulatory support system in use for the past 5 decades,<sup>5</sup> there is a need to improve patient outcomes either with new treatments or perhaps revised treatment protocols.

To this end, the IMPRESS Severe Shock trial researchers sought to determine whether the Impella CP device can reduce 30-day mortality (in MI patients) in comparison with an IABP. They looked specifically at the Impella CP device (maximum output around 3.7 L/min). The multicenter, randomized study included patients presenting with acute MI with ST-segment elevation complicated by severe cardiogenic shock in the setting of percutaneous coronary intervention (PCI). Patients were randomized at 1:1 to receive either the Impella device or an IABP. The primary study endpoint was 30-day all-cause mortality, with 6-month all-cause mortality set as a secondary endpoint.

## Trial Results

The researchers reported no significant differences between the two patient groups (50% IABP vs. 46% Impella;  $p = 0.92$ ) at 30 days, as well as no significant differences at 6 months (50% IABP vs. 50% Impella;  $p = 0.923$ ). They also reported that refractory cardiogenic shock was the cause of death in 29% of deceased patients (25% in the IABP group vs. 33% in the Impella group).

In the study, bleeding occurred more often in the Impella treated patients than in the IABP treated patients (33% vs. 8%). Higher rates of bleeding with Impella compared with IABP were also described in a registry comparing the two devices, that found severe bleeding in 26% of the Impella patients versus 6% of IABP patients. Two large multi-center Impella

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registries describe the rates of bleeding requiring transfusion of 24.2% and 17.5% and the rates of hemolysis as 7.5% and 10.3%.<sup>6</sup>

## What Does It All Mean?

Study co-primary investigator **Jose P.S. Henriques, MD, PhD**, of the Academic Medical Center at the University of Amsterdam, The Netherlands, noted that one of the important things to emphasize was the consecutive nature of patient enrollment. Patients in Europe and the Western world (i.e., the United States), Dr. Henriques said, were typically “resuscitated younger patients who stayed in hemodynamic demise despite angioplasty.”

One interesting finding of note from a sub-group analysis, showed a trend towards lower mortality rates in patients in whom either device was inserted before the primary PCI (25% vs. 52.5%). The trend toward improved outcomes when mechanical circulatory support is initiated prior to primary PCI has been seen in previous studies and registries (such as the USpella registry,<sup>7</sup> Abdel-Wahab et al.,<sup>8</sup> and Schwartz et al.<sup>9</sup>) Perhaps the use of higher-powered support is not as important as the time the

support is initiated. It may be time to revisit treatment protocols, to not only ensure IABP remains the first-line mechanical circulatory support device given its efficacy and safety profile but also to initiate hemodynamic support prior to PCI to further improve patient outcomes. ■

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